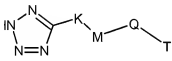


AMENDMENTS TO THE CLAIMS

The following Listing of Claims replaces all prior versions, and listings, of claims.

LISTING OF CLAIMS

1. (Currently Amended) A pharmaceutical composition comprising: insulin and a zinc-binding ligand which reversibly binds to a His^{B10} Zn²⁺ site of an insulin hexamer, wherein the ligand is



wherein K is a valence bond, C₁-C₆-alkylene, -NH-C(=O)-U-, -C₁-C₆-alkyl-S-, -C₁-C₆-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸,

U is a valence bond, C₁-C₆-alkenylene, -C₁-C₆-alkyl-O- or C₁-C₆-alkylene wherein any C₁-C₆-alkyl moiety is optionally substituted with C₁-C₆-alkyl,

R³⁸ is C₁-C₆-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R³⁹,

R³⁹ is independently selected from halogen, cyano, nitro, amino,

M is indolylene optionally substituted with one or more substituents independently selected from R⁴⁰,

R⁴⁰ is selected from: hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -NR⁴¹S(O)₂R⁴², -S(O)₂NR⁴¹R⁴², -S(O)NR⁴¹R⁴², -S(O)R⁴¹, -S(O)₂R⁴¹, -OS(O)₂R⁴¹, -C(O)NR⁴¹R⁴², -OC(O)NR⁴¹R⁴², -NR⁴¹C(O)R⁴², -CH₂C(O)NR⁴¹R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -CH₂OR⁴¹, -CH₂OC(O)R⁴¹, -CH₂NR⁴¹R⁴², -OC(O)R⁴¹, -OC₁-C₆-alkyl-C(O)OR⁴¹, -OC₁-C₆-alkyl-OR⁴¹, -S-C₁-C₆-alkyl-C(O)OR⁴¹, -C₂-C₆-alkenyl-C(=O)OR⁴¹, -NR⁴¹-C(=O)-C₁-C₆-alkyl-C(=O)OR⁴¹, -NR⁴¹-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, -C₂-C₆-alkenyl-C(=O)R⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl; C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, which may each optionally be substituted with one or more substituents selected from R⁴³, aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-

C₆-alkenyl, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴,

R⁴¹ and R⁴² are independently selected from hydrogen, -OH, C₁-C₆-alkyl, C₁-C₆-alkenyl, aryl-C₁-C₆-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R⁴⁵, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R⁴⁶, R⁴¹ and R⁴² when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R⁴³ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴¹, and -NR⁴¹R⁴²

R⁴⁴ is independently selected from halogen, -C(O)OR⁴¹, -CH₂C(O)OR⁴¹, -CH₂OR⁴¹, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴² and C₁-C₆-alkyl,

R⁴⁵ is independently selected from halogen, -CN, -CF₃, -OCF₃, -O-C₁-C₆-alkyl, -C(O)-O-C₁-C₆-alkyl, -COOH and -NH₂,

R⁴⁶ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl,

Q is a valence bond, C₁-C₆-alkylene, -C₁-C₆-alkyl-O-, -C₁-C₆-alkyl-NH-, -NH-C₁-C₆-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C₁-C₆-alkyl, -C(=O)-, or -C₁-C₆-alkyl-C(=O)-N(R⁴⁷)- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R⁴⁸,

R⁴⁷ and R⁴⁸ are independently selected from hydrogen, C₁-C₆-alkyl, aryl optionally substituted with one or more R⁴⁹,

R⁴⁹ is independently selected from halogen and -COOH,

T is: hydrogen; C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰, aryl, aryloxy, aryloxy-carbonyl, aryl-C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkoxy, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl-, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl, heteroaryl-C₂-C₆-alkynyl, wherein any alkyl, alkenyl, alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected

from R^{50} ,

R^{50} is C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, aryl, aryloxy, aryl- C_1 - C_6 -alkoxy, $-C(=O)-NH-C_1$ - C_6 -alkyl-aryl, $-C(=O)-NR^{50A}-C_1$ - C_6 -alkyl, $-C(=O)-NH-(CH_2CH_2O)_mC_1$ - C_6 -alkyl-COOH, heteroaryl, heteroaryl- C_1 - C_6 -alkoxy, $-C_1$ - C_6 -alkyl-COOH, $-O-C_1$ - C_6 -alkyl-COOH, $-S(O)_2R^{51}$, $-C_2$ - C_6 -alkenyl-COOH, $-OR^{51}$, $-NO_2$, halogen, $-COOH$, $-CF_3$, $-CN$, $=O$, $-N(R^{51}R^{52})$, wherein m is 1, 2, 3 or 4, and wherein the aryl or heteroaryl moieties are optionally substituted with one or more R^{53} , and the alkyl moieties are optionally substituted with one or more R^{50B} ,

R^{50A} and R^{50B} are independently selected from $-C(O)OC_1$ - C_6 -alkyl, $-COOH$, $-C_1$ - C_6 -alkyl- $C(O)OC_1$ - C_6 -alkyl, $-C_1$ - C_6 -alkyl-COOH, or C_1 - C_6 -alkyl,

R^{51} and R^{52} are independently selected from hydrogen and C_1 - C_6 -alkyl,

R^{53} is independently selected from C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, $-C_1$ - C_6 -alkyl-COOH, $-C_2$ - C_6 -alkenyl-COOH, $-OR^{51}$, $-NO_2$, halogen, $-COOH$, $-CF_3$, $-CN$, or $-N(R^{51}R^{52})$,

or any enantiomer, diastereomer, racemic mixture, tautomer, or salt thereof with a pharmaceutically acceptable acid or base.

selected from the group consisting of benzotriazoles, 3-hydroxy-2-naphthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, pyrimidinetriones, or 4-cyano-1,2,3-triazoles, or enantiomers, diastereomers, racemic mixtures, tautomers, or salts thereof with a pharmaceutically acceptable acid or base.

2. – 127. (Cancelled).

128. (Original) A pharmaceutical composition according to claim 127 wherein K is a valence bond, C_1 - C_6 -alkylene, $-NH-C(=O)-U-$, $-C_1$ - C_6 -alkyl-S-, $-C_1$ - C_6 -alkyl-O-, or $-C(=O)-$, wherein any C_1 - C_6 -alkyl moiety is optionally substituted with R^{38} .

129. (Original) A pharmaceutical composition according to claim 128 wherein K is a valence bond, C_1 - C_6 -alkylene, $-NH-C(=O)-U-$, $-C_1$ - C_6 -alkyl-S-, or $-C_1$ - C_6 -alkyl-O-, wherein any C_1 - C_6 -alkyl moiety is optionally substituted with R^{38} .

130. (Original) A pharmaceutical composition according to claim 129 wherein K is a

valence bond, C₁-C₆-alkylene, or -NH-C(=O)-U, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.

131. (Original) A pharmaceutical composition according to claim 130 wherein K is a valence bond or C₁-C₆-alkylene, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.

132. (Original) A pharmaceutical composition according to claim 130 wherein K is a valence bond or -NH-C(=O)-U.

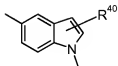
133. (Original) A pharmaceutical composition according to claim 131 wherein K is a valence bond.

134. (Original) A pharmaceutical composition according to claim 127 wherein U is a valence bond or -C₁-C₆-alkyl-O-.

135. (Original) A pharmaceutical composition according to claim 134 wherein U is a valence bond.

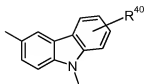
136. – 141. (Cancelled).

142. (Original) A pharmaceutical composition according to claim 141 wherein M is



143. (Original) A pharmaceutical composition according to claim 139 wherein M is carbazoylene optionally substituted with one or more substituents independently selected from R⁴⁰.

144. (Original) A pharmaceutical composition according to claim 143 wherein M is



145. (Currently Amended) A pharmaceutical composition according to claim 127 wherein R⁴⁰ is selected from: hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -S(O)₂R⁴¹, -NR⁴¹C(O)R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -C₂-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl, C₁-C₆-alkyl or C₂-C₆-alkenyl which may each optionally be substituted with one or more substituents independently selected from R⁴³, aryl, aryloxy, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, or heteroaryl-C₂-C₆-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴.

146. (Previously Amended) A pharmaceutical composition according to claim 145 wherein R⁴⁰ is selected from: hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -S(O)₂R⁴¹, -NR⁴¹C(O)R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -C₂-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl, C₁-C₆-alkyl or C₂-C₆-alkenyl which may each optionally be substituted with one or more substituents independently selected from R⁴³, ArG1, ArG1-O-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, ArG1-C₂-C₆-alkenyl, Het3, Het3-C₁-C₆-alkyl, or Het3-C₂-C₆-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴.

147. (Previously Amended) A pharmaceutical composition according to claim 146 wherein R⁴⁰ is selected from: hydrogen, halogen, -CF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -C(O)OR⁴¹, =O, or -NR⁴¹C(O)R⁴², C₁-C₆-alkyl, and ArG1.

148. (Original) A pharmaceutical composition according to claim 147 wherein R⁴⁰ is hydrogen.

149. (Previously Amended) A pharmaceutical composition according to claim 147 wherein R⁴⁰ is selected from: Halogen, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -C(O)OR⁴¹, or -NR⁴¹C(O)R⁴², Methyl, and Phenyl.

150. (Original) A pharmaceutical composition according to claim 127 wherein R⁴¹ and R⁴² are independently selected from hydrogen, C₁-C₆-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or -COOH.

151. (Original) A pharmaceutical composition according to claim 150 wherein R⁴¹ and R⁴² are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or -COOH.

152. (Original) A pharmaceutical composition according to claim 127 wherein Q is a valence bond, C₁-C₆-alkylene, -C₁-C₆-alkyl-O-, -C₁-C₆-alkyl-NH-, -NH-C₁-C₆-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C₁-C₆-alkyl, -C(=O)-, or -C₁-C₆-alkyl-C(=O)-N(R⁴⁷)- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R⁴⁸.

153. (Original) A pharmaceutical composition according to claim 152 wherein Q is a valence bond, -CH₂-, -CH₂-CH₂-, -CH₂-O-, -CH₂-CH₂-O-, -CH₂-NH-, -CH₂-CH₂-NH-, -NH-CH₂-, -NH-CH₂-CH₂-, -NH-C(=O)-, -C(=O)-NH-, -O-CH₂-, -O-CH₂-CH₂-, or -C(=O)-.

154. (Original) A pharmaceutical composition according to claim 127 wherein R⁴⁷ and R⁴⁸ are independently selected from hydrogen, methyl and phenyl.

155. (Previously Amended) A pharmaceutical composition according to claim 127 wherein T is: Hydrogen, C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁰, aryl, aryl-C₁-C₆-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

156. (Previously Amended) A pharmaceutical composition according to claim 155 wherein T is: hydrogen, C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁰, ArG1, ArG1-C₁-C₆-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

157. (Previously Amended) A pharmaceutical composition according to claim 156 wherein T is: hydrogen, C₁-C₆-alkyl, optionally substituted with one or more substituents independently selected from R⁵⁰, phenyl, phenyl-C₁-C₆-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

158. (Original) A pharmaceutical composition according to claim 157 wherein T is phenyl substituted with R⁵⁰.

159. (Original) A pharmaceutical composition according to claim 127 wherein R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, aryl-C₁-C₆-alkoxy, -C(=O)-NH-C₁-C₆-alkyl-aryl, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_m-C₁-C₆-alkyl-COOH, heteroaryl, -C₁-C₆-alkyl-COOH, -O-C₁-C₆-alkyl-COOH, -S(O)₂R⁵¹, -C₂-C₆-alkenyl-COOH, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, -CN, =O, -N(R⁵¹R⁵²), wherein the aryl or heteroaryl moieties are optionally substituted with one or more R⁵³.

160. (Original) A pharmaceutical composition according to claim 159 wherein R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_m-C₁-C₆-alkyl-COOH, aryl-C₁-C₆-alkoxy, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.

161. (Original) A pharmaceutical composition according to claim 160 wherein R⁵⁰ is C₁-C₆-alkyl, aryloxy, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_m-C₁-C₆-alkyl-COOH, aryl-C₁-C₆-alkoxy, -OR⁵¹, halogen, -COOH, -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.

162. (Original) A pharmaceutical composition according to claim 161 wherein R^{50} is C_1 - C_6 -alkyl, $ArG1-O-$, $-C(=O)-NR^{50A}-C_1-C_6$ -alkyl, $-C(=O)-NH-(CH_2CH_2O)_mC_1-C_6$ -alkyl-COOH, $ArG1-C_1-C_6$ -alkoxy, $-OR^{51}$, halogen, $-COOH$, $-CF_3$, wherein any aryl moiety is optionally substituted with one or more R^{53} .

163. (Original) A pharmaceutical composition according to claim 162 wherein R^{50} is $-C(=O)-NR^{50A}CH_2$, $-C(=O)-NH-(CH_2CH_2O)_2CH_2-COOH$, or $-C(=O)-NR^{50A}CH_2CH_2$.

164. (Original) A pharmaceutical composition according to claim 162 wherein R^{50} is phenyl, methyl or ethyl.

165. (Original) A pharmaceutical composition according to claim 164 wherein R^{50} is methyl or ethyl.

166. (Currently Amended) A pharmaceutical composition according to claim 127 wherein m is 1 or 2.

167. (Currently Amended) A pharmaceutical composition according to claim 127 wherein R^{51} is methyl.

168. (Currently Amended) A pharmaceutical composition according to claim 127 wherein R^{53} is C_1-C_6 -alkyl, C_1-C_6 -alkoxy, $-OR^{51}$, halogen, or $-CF_3$.

169. (Currently Amended) A pharmaceutical composition according to claim 127 wherein R^{50A} is $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-COOH$, $-CH_2C(O)OCH_3$, $-CH_2C(O)OCH_2CH_3$, $-CH_2CH_2C(O)OCH_3$, $-CH_2CH_2C(O)OCH_2CH_3$, $-CH_2COOH$, methyl, or ethyl.

170. (Currently Amended) A pharmaceutical composition according to claim 127 wherein R^{50B} is $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-COOH$, $-CH_2C(O)OCH_3$, $-CH_2C(O)OCH_2CH_3$,

-CH₂CH₂C(O)OCH₃, -CH₂CH₂C(O)OCH₂CH₃, -CH₂COOH, methyl, or ethyl.

171. – 204. (Cancelled)

205. (Original) A pharmaceutical composition according to claim 1 wherein the insulin is rapid acting insulin.

206. (Original) A pharmaceutical composition according to claim 1 wherein the insulin is selected from the group consisting of human insulin, an analogue thereof, a derivative thereof, and combinations of any of these.

207. (Original) A pharmaceutical composition according to claim 206 wherein the insulin is an analogue of human insulin selected from the group consisting of

- i. An analogue wherein position B28 is Asp, Lys, Leu, Val, or Ala and position B29 is Lys or Pro; and
- ii. des(B28-B30), des(B27) or des(B30) human insulin.

208. (Original) A pharmaceutical composition according to claim 207, wherein the insulin is an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro.

209. (Original) A pharmaceutical composition according to claim 207 wherein the insulin is des(B30) human insulin.

210. (Original) A pharmaceutical composition according to claim 207 wherein the insulin is an analogue of human insulin wherein position B3 is Lys and position B29 is Glu or Asp.

211. (Original) A pharmaceutical composition according to claim 206 wherein the insulin is a derivative of human insulin having one or more lipophilic substituents.

212. (Original) A pharmaceutical composition according to claim 211 wherein the insulin derivative is selected from the group consisting of B29-N^E-myristoyl-des(B30) human insulin, B29-N^E-palmitoyl-des(B30) human insulin, B29-N^E-myristoyl human insulin, B29-N^E-palmitoyl human insulin, B28-N^E-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N^E-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N^E-myristoyl-Thr^{B29} Lys^{B30} human insulin, B30-N^E-palmitoyl-Thr^{B29} Lys^{B30} human insulin, B29-N^E-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N^E-(N-lithocholyl-γ-glutamyl)-des(B30) human insulin, B29-N^E-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N^E-(ω-carboxyheptadecanoyl) human insulin.

213. (Original) A pharmaceutical composition according to claim 212 wherein the insulin derivative is B29-N^E-myristoyl-des(B30) human insulin.

214. (Original) A pharmaceutical composition according to claim 1 comprising 2-6 moles zinc²⁺ ions per mole insulin.

215. (Original) A pharmaceutical composition according to claim 214 comprising 2-3 moles zinc²⁺ ions per mole insulin.

216. (Original) A pharmaceutical composition according to claim 1 further comprising at least 3 molecules of a phenolic compound per insulin hexamer.

217. (Original) A pharmaceutical composition according to claim 1 further comprising an isotonicity agent.

218. (Original) A pharmaceutical composition according to claim 1 further comprising a buffer substance.

219. – 220. (Cancelled).